REMARKS/ARGUMENTS

I. PRELIMINARY REMARKS

Applicant thanks the Examiner for the Office Action of January 2, 2003, which has been studied with interest and care.

By this paper, the Specification, Abstract, and Claims have been amended.

II. AMENDMENTS TO CLAIM PRIORITY

In Paragraph 4 of the Office Action, the Examiner required that the specification be amended to contain specific references to the applications from which priority is claimed. By this Amendment, the specification has been appropriately amended.

III. REQUIREMENT FOR CERTIFIED COPY OF U.K. PRIORITY DOCUMENT

In Paragraph 5, the Examiner required under 35 U.S.C. 119(b) that a certified copy of the foreign application (U.K. application No. 9704876.3, filed November 8, 1997), be submitted. By the concurrently filed Submission of Foreign Priority Document and accompanying certified copy of the application, a certified copy of the foreign priority document has been submitted as required.

IV. OBJECTION TO THE DRAWINGS

In Paragraph 6, the Examiner objected to the drawings as informal. Applicant believes that the objection can be overcome by submission of a Petition to Accept Photographs as Drawings. The Examiner's confirmation of this would be appreciated. If the Examiner finds other aspects of the drawings objectionable, Applicant respectfully requests the Examiner to explain any additional bases for those objections, so that Applicant can understand the Examiner's position and respond fully and completely.

V. CONCISE STATEMENT OF THE RELEVANCE OF THE VON GIERKE REFERENCE

In Paragraph 8, the Examiner requested a concise statement of the relevance of the von Gierke reference in order for it to be considered. By the accompanying Concise Statement of the von Gierke reference, a concise statement of the relevance of the reference has been provided in order for the reference to be considered.

VI. MINOR ERRORS IN THE SPECIFICATION

In Paragraph 10 the Examiner stated that the specification has not been checked to the extent necessary to determine the presence of all possible minor errors, and requested Applicant's cooperation in correcting any errors of which Applicant may become aware in the specification.

In response, Applicant has checked the specification and is not aware of any errors. Inasmuch as the application is based on a British application, the British spellings have been used throughout (e.g., *haemoglobin* and *hybridisation* in paragraph [0009], *analysing* in paragraph [0021] , *coloured* in paragraph [0058] , etc.), but Applicant does not believe that using the British spellings constitutes errors. If Applicant becomes aware of any errors other than the use of British spellings, Applicant will correct those errors.

VII. AMENDMENT TO THE ABSTRACT

The Examiner has objected to the use of the word "said" in the Abstract. In response, Applicant has submitted a new Abstract which does not include the word "said" and which is directed toward the invention claimed in Claim 2. Applicant believes that the Abstract as currently submitted complies with all requirements for an Abstract.

VII. REJECTIONS OF THE CLAIMS

A. REJECTION OF CLAIMS 2, 6, AND 7 UNDER 35 U.S.C. 112

Claims 2, 6, and 7 are rejected under 35 U.S.C. 112 as being indefinite.

Claim 2 – "Cell Surface Exposed Component." Regarding Claim 2, the Examiner contends that the phrase "cell surface exposed component" is indefinite.

In response, Applicant submits that the phrase "cell surface exposed component" is both clear and easily understandable by a person of ordinary skill in the art. A component which is exposed on the surface of embryonic or fetal red blood cells can readily be determined by a person of ordinary skill in the art, for example by techniques that do not involve the disruption of the cell membrane. This can be done, for example, using antibodies to detect cell surface antigens (see, e.g., Paragraphs [0059] to [0066]), fluorescent markers (see, e.g., Paragraph [0058]), enzyme markers (see, e.g., Paragraph [0056]), and histochemical methods (see, e.g., Paragraph [0056]). The only requirement is that the cells have to be intact in order to show components are cell-surface exposed. Such techniques are well within the routine ability of a person of ordinary skill in the art. See generally the discussion in paragraphs [0050] to [0066].

Claims 6 and 7 – "Component" vs. "Adult Liver Component." With respect to claims 6 and 7, the Examiner suggests that the claims be amended to recite "adult liver component" consistently to make it clear that that is the "component" being referred to.

In response, Applicant has amended the claims in accordance with the Examiner's suggestion, and thanks the Examiner for the guidance provided.

Claim 7 – "At Less than 1 Percent on a Per Cell Basis." With regard to claim 7, the Examiner contends that the phrase "at less than 1 percent on a per cell basis" is indefinite, and suggests that if Applicant intends to claim a unit of measurement, it should be recited as such.

In response, Applicant submits that the term "at less than 1 percent on a per cell basis" is clear and easily understandable by a person of ordinary skill in the art. It simply means that the ratio of (number of adult liver component cells) / (number of embryonic or fetal red blood cells) is less than one percent. The unit of measure is number of cells, as stated. If the unit of measure were weight, or volume, the ratio would be expressed as "on a weight basis" or "on a per volumetric basis," respectively. Because the unit of measure is the number of cells, the ratio is expressed "on a per cell basis" as recited. Accordingly, Applicant respectfully submits that the claim language is clear and definite.

B. DOUBLE PATENTING REJECTION

Claims 2, 6, 9, 10, and 12 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 6,331,395, which is the parent of this application and which is commonly owned.

In response, Applicant agrees to submit a Terminal Disclaimer in the event that the other bases for rejecting the claims are overcome. In any event, Applicant expects to submit a Terminal Disclaimer shortly.

C. REJECTION OF CLAIMS 2-4 AND 6 AS ANTICIPATED UNDER 35 U.S.C. 102(b) BY *BINACHI ET AL.*

Claims 2-4 and 6 are rejected under 35 U.S.C. 102(b) as being anticipated by Bianchi et al. (WO 91/07660) (hereinafter, *Bianchi)*

Applicant respectfully disagrees. Claim 2 recites a method of isolating embryonic or fetal red blood comprising "determining which cell or cells contain or express an adult liver component that is a cell surface exposed component, wherein the adult liver component is not transferrin receptor, the method comprising the steps of:

(a) contacting the sample with a reagent that specifically binds the adult liver component;

(b) allowing the reagent to bind to the adult liver component; and . . . "

(emphases added). *Bianchi* does not disclose or suggests these steps. Nowhere does *Bianchi* mention an *adult liver component*, and the Examiner has not even contended that *Bianchi* discloses such a limitation.

In the parent application, the Examiner had contended that CD45 is an adult liver component. It is important to note that CD45 is not an adult liver component.

Lavabre-Bertrand et al (1994) *Leukaemia* (8)(3), 402-408 was previously cited by the Examiner (in the office action dated January 18, 2001 in the parent application USSN 09/392,055) as indicating that CD45 is an adult liver component. Applicant respectfully submits

that the Examiner was mistaken; *Lavabre-Bertrand* shows that CD45 is expressed in fetal liver, not in adult liver.

As previously noted by the Examiner, *Lavabre-Bertrand* shows that CD45 expression is detected in low levels when measured in immature cells but expression increases with cell maturity (page 402, second column, second paragraph). However, this observation is confined to bone marrow cells, which are haematopoietic blood cell precursors (as is also apparent from the first paragraph of the Discussion (page 407) and the paragraph spanning pages 407 and 408). It cannot be extrapolated, as Applicant believes the Examiner has done, for all cell types, for example liver. In the fetus, the major haemopoietic organ is not bone marrow but is situated within the fetal liver and hence can be regarded as a component of fetal liver. This is compatible with the expression of CD45 antigen in fetal liver (see Figure 5 on page 406 of Lavabre-Bertrand). In contrast, in late fetal life and early infancy there is a transition to bone marrow being the major haemopoietic organ and progressive reduction in the contribution by liver. By late infancy the human liver is not a haemopoietic organ. Hence adult liver does not express haemopoietic antigens and CD45 cannot therefore be termed an adult liver component.

The Examiner had also referred to Figure 2 on page 404 lf *Lavabre-Bertrand* as showing CD45 expression. However, this Figure actually shows CD24 expression, as is clear from the figure legend. The Examiner was correct that Table 1 shows CD45 expression in bone marrow, liver and spleen; however, this is fetal tissue, not adult tissue.

The Examiner will note that WO 91/07660 contemplates using the antibody to CD45 for eliminating maternal leucocytes, as it binds to maternal leucocytes but not to fetal nucleated erythrocytes (see page 10, line 27 to page 11, line 7 and Example 1, for example page 23, lines 15 to 31). There is no isolation of the embryonic or fetal red blood cells by virtue of being bound to the anti-CD45 reagant. The use taught by WO 91/07660 for antibodies to CD45 is the elimination of contaminating maternal leucocytes (see page 10, lines 21 to 26 and page 11, lines 4 to 6), whereas the use taught for antibodies to the transferrin receptor (which is explicitly excluded) is binding to the fetal nucleated cells (see page 11, lines 15 to 19 and page 30, lines 20 to 30). It is clear from page 17, lines 25 to 28, that anti-Leu3 and anti-Leu4 also bind to maternal cells but not fetal nucleated cells.

In order to reject a claim as anticipated under 35 U.S.C. 102(b), all limitations must be met exactly in the reference. The limitations recited are not disclosed or suggested by the *Bianchi* reference, nor the *Lavabre-Bertrand* reference previously cited. Accordingly, claim 2 is not anticipated by the reference, nor is it rendered obvious by the reference. Similarly, claims 3-4 and 6, which depend from claim 2, are patentable for at least the same reasons.

D. REJECTION OF CLAIMS 2-4 AND 6 AS ANTICIPATED UNDER 35 U.S.C. 102(b) BY *SPECTOR ET AL*

Claims 2-4 and 6 are further rejected under 35 U.S.C. 102(b) as being anticipated by Spector et al. (Am J. Hum Genet. 32:79-87, 1980) (Hereinafter, "*Spector*"). The Examiner contends that "*Spector* show[s] the identification and isolation of a specific adult liver component (Arginase)."

Applicant respectfully disagrees. Firstly, arginase is not an "adult liver component" as defined in the specification. ("By 'adult liver component' we mean a component of an adult liver cell which is predominantly associated with the adult liver and, if it is found at all in other tissues of the adult, it is either found at low levels in that other tissue compared to the liver or that the mass of the other tissue in which the said component is found, compared to the mass of the liver, is low so that the total amount of the adult liver component is higher in the whole liver compared to the total amount in the whole other tissue." Paragraph [0007].). Further, it is cytosolic, as opposed to a cell surface exposed component, and the requirement in the claims that the adult liver component is a cell surface exposed component is described in the specification. Accordingly, arginase as disclosed in *Spector et al.* does not satisfy the requirements set out in the present claims, and *Spector et al.* therefore cannot anticipate the claims.

Applicant agrees with the Examiner (in the Office Action dated January 18, 2001 in the parent application) that *Spector* evaluated activities, heavy metal requirements, heat stability, pH optimum, kinetic properties and anti-arginase binding reactions, and found that "both enzyme species were either identical or substantially similar by all criteria." Clearly, this means that arginase activities or anti-arginase antibodies cannot be used to differentiate between fetal and adult cells, because it is identical in fetal and adult cells, as previously discussed in Applicant's

response dated October 27, 2000 to the Office Action dated May 1, 2000 in the parent application.

The Examiner previously concluded that *Spector* is considered to "teach the utility of an antibody directed against fetal red blood cells in a mixture containing 5% fetal cells and 95% maternal cells in order to produce a solution containing 95% fetal cells (see page 86)." This conclusion is flawed because the antibody used to effect this separation was not an anti-arginase antibody, as appears to have been assumed by the Examiner. No separation using an anti-arginase antibody is described in *Spector*. The passage referred to by the Examiner is merely a reference to a previous description of the use of an anti-i antiserum/antibody (Kan et al. (1974) *Blood* 43, 411-415). Anti-i antibody is a powerful antibody isolated from a patient with cold-antibody haemolytic anaemia (Wiener et al. (1956) *Am. Intern. Med.* 44, 221; Marsh (1961) *Br. J. Haematol.* 7, 200-209) in 1956. This antibody is an agglutinin to Factor I on red blood cells. Factor I is not a liver component but a component of red blood cells, and the anti-i antibody is therefore not a reagent that specifically binds an adult liver component. In particular, Miyake et al (1989) *Cancer Research* 49, 5689-5695 show that anti-i antibodies react with a variety of tumors but do not react with the majority of normal adult tissues. However, they do react with pancreatic duct epithelia, lung bronchial gland epithelia, placenta and granulocytes. They also state that the anti-i antigen is present in a number of fetal tissues as well as fetal erythrocytes. It is clear that expression of anti-i is onco-developmentally regulated and therefore confined to fetally derived tissues and to tumors. Anti-i is therefore not an adult liver component, and the claims are not anticipated by *Spector*.

E. REJECTION OF CLAIMS 5, 7, 9-12, AND 14-16 AS OBVIOUS UNDER 35 U.S.C. 103(a)

Claims 5, 7, 9-12, and 14-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Bianchi et al.* (WO 91/07660) or *Spector et al.* (*Am J. Hum. Genet.* 32;79-87, 1980) in view of *Hume et al.* (*Early Human Development*, Vol. 42, No. 2, 1995, pp. 85-95) and *Hume et al.* (*Blood*, Vol. 871, No. 2, 1996, pp. 762-770).

The Examiner appears to be confusing the issues (1) of how fetal cells can be isolated from maternal blood, and (2) what analysis can usefully be performed on fetal cells (which may

be obtained from the placenta or from a fetal blood vessel on the chorionic plate (for example *Spector*, or identified in or isolated from maternal blood (for example *Pazouki et al.*)). Components which may be investigated in fetal cells are not necessarily suitable for use in identifying or isolating fetal cells from maternal blood. Identification of a component as a target suitable for investigation in fetal cells does not imply that the component is suitable for use in identification or isolation of fetal cells. For example, components which may be suitable for investigation in fetal cells need not be absent from maternal blood cells, whereas a component (such as arginase, as discussed above) that is present in both fetal cells and maternal blood cells is not suitable as a basis for distinguishing or separating fetal cells from maternal cells.

Hume et al. (1995) and *Hume et al.* (1996) provide no suggestion that a cell surface exposed adult liver component would be suitable for use in a method for isolating fetal cells as claimed.

Firstly, the components identified in *Hume et al.* (1995) and *Hume et al.* (1996) are not "cell surface exposed components" (as required by the present claims), and the documents suggest the investigation of further endoplasmic reticulum (intracellular) components, as noted by the Examiner. Thus, the reference teaches away from the invention as claimed.

Further, *Hume et al.* 91995) and *Hume et al.* (1996) are not concerned at all with whether the presence of the investigated intracellular components allow fetal cells to be distinguished from maternal blood cells, much less allow them to be isolated; they are concerned with whether potential defects of the adult liver can usefully be investigated in fetal blood cells, which are more easily accessible than other fetal cells. The references are not concerned at all with the details of how fetal cells may be isolated from maternal blood as claimed; rather, they are concerned with how the isolated cells may be investigated and the utility of such investigation. The references would not be considered by a person of ordinary skill seeking to improve fetal cell isolation because the reference provide no new teaching whatsoever on the subject of fetal cell isolation as claimed.

Similarly, *Spector* is also not concerned with the details of how fetal cells may be isolated from maternal blood; as for *Hume et al.* (1995) and *Hume et al.* (1996), they are concerned solely with how fetal cells may be investigated. There is no new teaching whatsoever on the subject of fetal cell isolation. The combination of *Spector* with either of the *Hume* references does not provide any new methods for isolating fetal cells, and in particular does not provide the claimed invention.

As noted above, WO 91/07660 does not suggest that a cell surface exposed adult liver component would be suitable for use in a method for isolating fetal cells. The combination of WO 91/07660 with *Hume et al.* (1995) or *Hume et al.* (1996) does not provide any new methods for isolating fetal cells, an in particular does not provide the claimed invention.

Accordingly, the claims as presented are allowable over the cited prior art.

CONCLUSIONS

For the foregoing reasons, Applicant submits that all of the claims as currently presented are allowable over the prior art. Early notice of allowance of the claims is earnestly solicited.

Respectfully submitted,

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